REMARKS/ARGUMENTS

First, Applicants would like to thank Examiners Long Le and Jacob Cheu for the courtesies extended during the telephonic interview conducted on October 12, 2005.

In response to the Office Action of September 08, 2005, Applicants request re-examination and reconsideration of this application for patent pursuant to 35 U.S.C. 132.

Claim Status/Support for Amendments

Claims 1, 39-46 are currently pending. Claims 39 and 42 have been amended herein. Claims 2-38 were cancelled in a previous response. Claim 39-46 remain pending. As discussed during the aforementioned telephonic interview of October 12, 2005, examined claim 1 (Group I) has been deemed to be allowable by the Examiner. Claims 39-46 are drawn to the non-elected invention. Applicants respectfully request rejoinder of the remaining claims (39-46), in accordance with the decision in *In re Ochiai*, since the remaining claims (39-46) are limited to the use of the biopolymer markers of claim 1 (the examined claim of the elected Group I invention). If the biopolymer marker peptide of claim 1 is found to be novel, methods and kits limited to its use should also be found novel.

No new matter has been added by the amendments to the claims made herein.

Claim 39 has been amended in response to suggestions made by the Examiner during the telephonic interview of October 12, 2005. For the sake of clarity "in a manner effective to maximize elucidation of discernible" in claim 39, step (b) has been replaced with --to elucidate--. Support for this amendment can be found throughout the specification as originally filed, see, for example page 35, lines 19-22.

Claim 42 has been amended to define the acronyms for the recited mass spectrometry procedures. These acronyms are well known to those of skill in the art and are defined in various parts of the specification as originally filed, see, for example page 10, lines 2-11.

Drawings

Applicants have provided the Examiner by way of FEDEX express, mailed on October 19, 2005, a Declaration under 37 CFR § 1.132 with attached Figure (entitled "HiQ 1 -(Elusion) Insulin Resistance vs. Normal"), which represents replacement Figure 1. The Examiner asserts in the rejection of claim 1 under 35 USC 112 (first paragraph), discussed below, the results of the photograph in original Figure 1 are "vague and fuzzy" with only one band appearing on one of the insulin resistance patients. As discussed in the aforementioned Declaration, replacement Figure 1 is provided

to more clearly show Band #3 corresponding to betaine/GABA transport protein fragment (SEQ ID NO:2); the biopolymer marker as currently claimed is clearly present in the different insulin resistance patients (lanes 3 and 4; as read from the left). Replacement Figure 1 is merely a duplicate of the original gel made at the time the experiments disclosed in the instant specification were first carried out, thus, replacement Figure 1 presents no new matter into the specification as filed.

Rejection under 35 USC 112, first paragraph

Claim 1, as filed on July 29, 2005, stands rejected under 35 USC 112, first paragraph, as allegedly failing to comply with the enablement requirement. The Examiner asserts that the claim contains subject matter which was not described in the specification in a such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The Examiner now asserts that the instant invention would not enable one of ordinary skill in the art to use this invention without undue experimentation. The Examiner posits that in view of the mass spectral profile of the peptides as in Figures 2 and 3, there is no explanation or illustration of the significance or relationship between the peptide fragments, i.e., SEQ ID NO:2, and

insulin resistance.

The Examiner further asserts the current data in Figure 1 does not demonstrate "up-regulation" phenomena in the insulin resistance patients. The Examiner points to Figure 1 containing the two samples from insulin resistance patients (second and third lane from the left [sic]). The results of the gel electrophoresis are allegedly vague and fuzzy and show only one band vaguely appearing on one of the insulin resistance patients (see lane two of Figure 1). Thus, the Examiner concludes there is no consistency among the insulin resistance patients if the appearance of a fragment peptide (up-regulation) is significant and essential as a biomarker for this specific disease.

Applicants respectfully disagree with the Examiner's interpretation of the claimed invention and submit that the Examiner's assertion regarding lane 2 is incorrect and may have caused the Examiner to misinterpret the results shown in the gel electrophoresis of original Figure 1. Lane 1 is reserved for low molecular weight standards. Lane 2 (as read from the left) corresponds to a diabetes type I patient, not an insulin resistance patient as stated by the Examiner in the instant Office action (see original and replacement Figure 1). Lanes 3 and 4 contain samples obtained from different insulin resistance patients. Lanes 5 and 6 contain sample from Type II diabetes patients. Lanes 7 thru 9

correspond to sample obtained from normal control patients and lane 10 is reserved for high molecular weight standards, as disclosed along the perimeters of the photograph in original Figure 1 and replacement Figure 1.

Band #3 corresponds to betaine/GABA transport protein. The identified betaine/GABA transport protein fragment weighs about 1211.5591 daltons and corresponds to the biopolymer marker that is currently claimed (SEQ ID NO:2), see page 46, lines 4-10. Band #3 appears in both insulin resistance patients, that is, lanes 3 and 4, respectively (see replacement Figure 1). Band #3 was resolved from the gel that is pictured in Figure 1. Thus, contrary to the Examiner's assertion, replacement Figure 1 does demonstrate "up regulation" phenomena in the insulin resistance patients.

In the interest of furthering prosecution, Applicants filed a Declaration under 37 CFR § 1.132 (October 19, 2005) with attached Figure entitled "HiQ 1 -(Elusion) Insulin Resistance vs. Normal" which now clearly shows a comparison of the protein content of samples obtained from patients having a history of insulin resistance or Type I diabetes with the protein content of samples obtained from patients determined to be normal with regard to insulin resistance and diabetes. Band #3 is clearly decipherable in lanes 3 and 4 (as read from the left) of replacement Figure 1,

as resolved from a sample obtained from a patient with a history of insulin resistance and can be identified as differentially expressed between a disease state (insulin resistance) and a non-disease state (normal). Subsequently Band #3 was excised from the gel and subjected to mass spectrometry (TOF MS/MS; Figures 2 and 3). The resulting mass spectral profile of the currently claimed SEQ ID NO: 2 (Figure 2) was then compared with a database of the sequences of known peptides and the profile identified as a fragment of the betaine/GABA transport protein.

Considering that the betaine/GABA transport protein fragment (SEQ ID NO:2) was identified by differential expression between insulin resistance and normal, it is indicated as a potential disease marker for insulin resistance. The mass spectral profile of SEQ ID NO:2 as shown in Figure 2, as established by the instant invention, can be used as a reference for comparison with test samples. Accordingly, the presence of the mass spectral profile of SEQ ID NO:2 in a sample can potentially identify insulin resistance in the patient from which the sample was obtained, i.e. Figure 2 represents insulin resistance patients.

Thus, contrary to the Examiner's assertions, the instant specification does explain and illustrate the relationship between the claimed peptide fragments and insulin resistance.

The "test of enablement" is whether one reasonably skilled in

the art could make or use the invention from the disclosures in the patent coupled with information known in the prior art without undue experimentation (see MPEP 2164.01) and/or a statement of utility in the specification contains within it a connotation of how to use, 35 USC 112, is satisfied (see MPEP 2164.01(c)).

Furthermore, the decision in *In re Brandstadter* (179 USPQ 286; MPEP 2164.05) has established that the evidence provided by applicant (to overcome an enablement rejection) need not be conclusive but merely convincing to one of skill in the art.

The Examiner appears to provide as evidence of lack of enablement in the instant specification a recent article (Zhang et al., Neurobiology of Aging, Vol. 26, page 207 (2005)), wherein the Examiner believes the authors conducted studies using similar methods as described in the instant invention, i.e., proteomic approaches for two-dimensional gel differential electrophoresis coupled with mass spectrometry analysis. The study by Zhang et al., was aiming to identify biomarkers of common age-related neurodegenerative disease. The authors identified around 30 proteins with >20% change in concentration between older and younger individuals. According to the Examiner, Zhang et al., do not conclude that these proteins as biomarkers, rather, Zhang et al., suggest the data of those proteins are a "value platform" and invite further experimentation and confirmation (see page 214,

right column, second paragraph; left column, last paragraph).

Applicants respectfully disagree with the Examiner's reliance on the article by Zhang et al.

As noted by the Examiner, Zhang et al., was published in 2005 (received October 2003), which is more than 3 years after the filing date of the instant invention (November 21, 2001), thus, Applicants believe the reference is not relevant to the state of the art existing at the filing date of the application and cannot be used to determine whether the instant disclosure is enabled as of the filing date. It has been established that, in general, the Examiner *should not* use post-filing date references to demonstrate the patent is non-enabling (see MPEP 2164.05(a)).

Assuming, *in arguendo*, Zhang et al., is a valid reference the mere fact that something has not been done clearly is not, in itself, a sufficient basis for rejecting all applications purporting to disclose how to do it (see MPEP 2164.02).

Applicants assert that upon closer inspection the study of Zhang et al., do not parallel the methods disclosed in the instant invention. Zhang et al., used a "shotgun" proteomic approach coupled with liquid chromatography followed by mass spectrometry to identify proteins in human CSF (see abstract; page 208, left column, last paragraph). Specifically, the method of Zhang et al. used pooled CSF samples from 22 younger and 16 older subjects to

generate two pooled samples for proteomic analysis (page 208, right column, penultimate paragraph). Zhang et al., acknowledges the problem with the use of pooled CSF samples is that they were unable to determine if the differences found were due to age-related changes in a single individual, only few individuals or distributed over all participants (page 214, last paragraph).

The claimed methodology of the present invention does not use pooled samples, rather, a sample from an individual patient is obtained and at least one biopolymer marker sequence is isolated from the sample and compared to the biopolymer marker sequence as disclosed in the present invention. Unlike Zhang et al., the presence of the mass spectral profile of SEQ ID NO:2 of the instant invention in a sample can potentially identify insulin resistance in the patient from which the sample was obtained, see for example, page 46, line 17 to page 47, line 5.

The Zhang et al., publication states the aging *markers* (30 identified proteins) need to be validated (page 211, right column 2nd full paragraph). Only two proteins (agrin and hnBNPm) were then identified individually by Western blot analysis. Zhang et al., refers throughout the publication to these proteins (agrin, hnBNPm) as "protein markers", see, for example page 211, right column, 2nd full paragraph, lines 1-6 and last line; page 214, right column, lines 2-4. Thus, contrary to the Examiner assertion, Zhang et al.,

do refer to these identified proteins as potential markers, but invites further study. Therefore, Zhang et al., actually supports and validates Applicants' study.

Thus, Applicants respectfully submit that the Zhang et al., reference is not applicable to the instant invention and does not control the question of enablement.

Applicants respectfully submit that many of the methods disclosed in the instant specification are routinely practiced in the field of proteomics by those of ordinary skill in the art attempting to identify biomarkers of particular physiological states.

For example, Scott D. Patterson presents the state of the art in mass spectrometry/proteomics by summarizing the Asilomar Conference on Mass Spectrometry (see attached article, Physiological Genomics 2:59-65 2000; reference 1). This conference took place in 2000, thus coinciding with the time that the instant inventors were working to develop the instant invention. For example, at page 64, left column of Patterson is a description of the SELDI approach (as discussed at the conference by Scot Weinberger) wherein defined chemical/biochemical surfaces are utilized to allow fractionation of proteins from biological fluids in a reproducible manner. This reproducibility allows comparisons between different samples to be made. Weinberger described a search

for markers of benign prostate hyperplasia that, like prostate cancer, displays elevated prostate specific antigen (PSA) levels. The fraction exhibiting a difference between these samples was able to be enzymatically digested, and a number of peptides were generated. These peptides were able to be fragmented using the MALDI-Qq-TOF (a procedure described by Ken Standing at the conference, page 62, left column of Patterson). It was found that there appears to be a difference in the relative level of seminogelin fragments between these two states (prostate cancer and benign prostatic hyperplasia), thus providing a potential differential marker.

Applicants respectfully draw the Examiner's attention to the fact that the method described by Weinberger is analogous to the method described in the instant specification. Furthermore, when interpreting data Weinberger uses the same approach to interpretation as the instant inventors in order to identify seminogelin fragments as a potential marker to distinguish between benign prostate hyperplasia and prostate cancer based on differential expression of the fragments. Additionally, Applicants respectfully point out to the Examiner that Weinberger linked differential expression of seminogelin to benign prostate hyperplasia and prostate cancer without analysis of a sample from a control patient free of disease or analysis of a sample from a

patient having another disease, which is not benign prostate hyperplasia or prostate cancer. Such linking of markers with disease through differential expression is commonly practiced in proteomics.

Considering the above comments, it is clear that both the specification and the prior art disclose how to make and use the instant invention. Accordingly, Applicants respectfully contend that the instant invention satisfies the "test for enablement" since one skilled in the art could make or use the invention from the disclosures in the specification coupled with information known in the prior art without undue experimentation and the specification contains within it a connotation of how to use.

The instant application discloses a method for diagnosing insulin resistance through the detection of the claimed biopolymer marker, SEQ ID NO:2. The data presented in Figures 1, 3 clearly show a positive correlation between the claimed biopolymer marker and insulin resistance. These bipolymer markers have not previously been shown to be associated with insulin resistance. When a marker is discovered to be associated with a disease state, its potential for diagnostics and/or therapeutics is immediately recognized, even if the involvement of the marker in disease pathology is unknown.

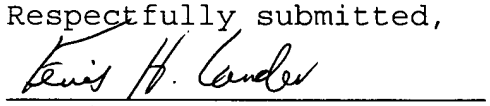
As shown by the above arguments, the instant specification

contrary to the Examiner's opinion, does contain proper guidance to enable one of ordinary skill in the art to practice the claimed method for diagnosing insulin resistance without undue experimentation. Thus, the Examiner's argument is not sufficient to support the enablement rejection; since the association of the claimed bipolymer marker, SEQ ID NO:2, with insulin resistance carries with it a connotation of use for diagnostics. Thus, Applicants respectfully request that this rejection under 35 USC 112, first paragraph now be withdrawn.

CONCLUSION

In light of the foregoing remarks, amendments to the specification, and amendments to the claims, it is respectfully submitted that the Examiner will now find the claims of the application allowable. Favorable reconsideration of the application is courteously requested.

Respectfully submitted,



Ferris H. Lander
Registration # 43,377

McHale & Slavin, P.A.
2855 PGA Boulevard
Palm Beach Gardens, FL 33410
(561) 625-6575 (Voice)
(561) 625-6572 (Fax)

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